REMARKS

Reconsideration of this application is respectfully requested. Claims 85-87 and 101 have been canceled. New claims 102-112 are derived from the canceled claims and are fully supported by the specification, for example, on pages 11-18. This amendment adds no new matter. New claims 102-112 read on the elected invention.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 85-87 and 101 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner contends that it is unpredictable as to what particular substitutions can be made to any particular molecule and result in a mutant analogue molecule with the functional attributes recited in the claims. (Office Action at 2.)

Applicant traverses the rejection for the reasons set forth previously in the response filed June 18, 2008. Moreover, Applicant has canceled claim 85-87 and 101 and added new claims 102-112, which recite that the analog is made by substituting one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes selected from ovalbumin, hen egg lysozyme, tetanus toxoid, or diphtheria toxoid T-cell epitopes and that the tertiary structure of the self protein is essentially preserved such that said analog induces an autoantibody response as evidenced by antibody binding to the unmodified self-protein.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduc-

tion to practice. *Regents of the Univ. of Cal. v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The specification may describe an actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim and determined that the invention would work for its intended purpose. *Cooper v. Goldfarb*, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998). Applicant's specification describes several actual reductions to practice of the claimed method.

Applicant's specification describes a method for inducing autoantibodies against a self-protein, providing two working examples of self-proteins, ubiquitin (Examples 1-2 & 5-6) and TNFα. (Examples 3-4 & 7-9) Applicant's specification describes a number of different analogues of ubiquitin and TNFα made by molecular biological means. (*Id.* at 11-13.) In these working examples, the analogues were made by substituting peptide fragments in ubiquitin and TNFα with a corresponding number of immunodominant foreign T-cell epitopes from ovalbumin or hen egg lysozyme. (*Id.*) The analogues were constructed such that the tertiary structure of the self proteins was essentially preserved such that the analogues induced autoantibody responses as evidenced by antibody binding to the unmodified self-proteins. (*Id.*) The specification further describes that other T-cell epitopes from tetanus toxoid or diphtheria toxoid can similarly be used in the claimed method. (*Id.* at 4, last paragraph; at 18, first paragraph; and at 19, original claim 5.) Applicant's reductions to practice satisfy the written description requirement for the claimed invention.

In addition, Applicant's description need only describe in detail that which is new or not conventional. *See Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed Cir. 1986). This is equally true whether the claimed invention is directed to a product or a process. M.P.E.P. § 2163. Applicant has described the new facets of the claimed invention, namely, the substitution of foreign T-cell epitopes into self-proteins and the production of autoantibodies against the self-protein. Applicant need not describe all self-proteins, since these are well-known in the art.

MPEP § 2163 indicates that a proper analysis for fulfilling the written description requirement under 35 U.S.C. § 112, first paragraph, requires the Examiner to:

> Determine whether the application as filed describes the complete structure (or acts of a process) of the claimed invention as a whole. The complete structure of a species or embodiment typically satisfies the requirement that the description be set forth "in such full, clear, concise, and exact terms" to show possession of the claimed invention.

Applicant's specification as filed describes the complete acts of the claimed method as a whole by providing multiple working examples of the claimed invention. The skilled artisan could immediately envision a plethora of additional analogues that would work in the claimed method based on Applicant's teachings. Accordingly, Applicant has shown possession of the claimed invention. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 85-87 and 101 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in the recitation of the phrase "tertiary

structure of the self protein is essentially preserved" because it is unclear what changes to the tertiary structure would or would not be encompassed. (Office Action at 5.) Applicant traverses the rejection.

Applicant submits that he skilled artisan would understand what changes to the tertiary structure of the self-protein would or would not be encompassed by the pending claims. The recitation that the "tertiary structure of the self protein is essentially preserved" cannot be read in a vacuum, but must be read in light of the recitation that the T-cell epitope is ***substituted*** into the self-protein and the recitation that the tertiary structure must be preserved to an extent that the analog is still capable of inducing an autoantibody response as evidenced by antibody binding to the unmodified self-protein.

The key to the preservation of the tertiary structure of the self-protein is the ***substitution*** of self-protein fragments with T-cell epitopes. This substitution preserves the overall secondary and tertiary structure of the self-protein to a large extent. (Specification at 3, lines 26-30.) It is the deletion of the self-protein sequences followed by the ***substitution*** of these sequences that minimally obscures the tertiary structure of the self-protein. (*Id.* at 10, lines 9-11.) Thus, it is the ***substitution*** of self-protein sequence with a T-cell epitope that preserves the tertiary structure of the self-protein. This renders the analog highly immunogenic. (*Id.* at 5-6, bridging sentence.) Thus, Applicant's claims encompass ***substitutions*** of self-protein sequences with T-cell epitopes. Accordingly, Applicant submits that the pending claims are definite and respectfully requests withdrawal of the rejection.

Claim 86 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in the recitation of the phrase "preserve N-terminal and C-terminal flanking regions" because it is unclear what changes to a molecule would be encompassed by the phrase. (Office Action at 7.) Applicant traverses the rejection for the reasons set forth previously in the response filed June 18, 2008. Moreover, Applicant has canceled claim 86 and added new claims 102-112. Claims 102-112 do not recite this phrase. Accordingly, the rejection is moot.

Claims 85-87 and 101 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in the recitation of the phrase "pathogenic self-protein" because it is unclear what changes to a molecule would be encompassed by the phrase. (Office Action at 7.) Applicant traverses the rejection for the reasons set forth previously in the response filed June 18, 2008. Moreover, Applicant has canceled claim 85-87 and 101 and added new claims 102-112. Claims 102-112 do not recite this phrase. Accordingly, the rejection is moot.

Rejections under 35 U.S.C. § 102(b)

Claims 85 and 86 were rejected under 35 U.S.C. § 102(b) as being anticipated by Russell-Jones et al. (WO 92/05192) as evidenced by Dean et al. (U.S. Patent 5,716,596). The Examiner contends that Russell-Jones et al. teaches Trat T-cell epitopes are inserted into proteins, wherein the insertion of the peptides increases the antibody response into which the Trat peptide has been inserted. (Office Action at 5.)

Applicant traverses the rejection for the reasons set forth previously in the response filed June 18, 2008. Moreover, Applicant has canceled claims 85 and 86 and added new claims 102-112, which recite that the analog is made by substituting one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes selected from ovalbumin, hen egg lysozyme, tetanus toxoid, or diphtheria toxoid T-cell epitopes. Russell-Jones et al. does not teach the substitution of any of the recited T-cell epitopes into a self-protein. Thus, Russell-Jones et al. cannot anticipate new claims 102-112. Accordingly, Applicant requests withdrawal of the rejection.

Rejections under 35 U.S.C. § 103(a)

Claims 85-87 were rejected under 35 U.S.C. § 103(a) as being obvious over Russell-Jones et al. (WO 92/05192) in view of Dean et al. (U.S. Patent 5,716,596). The Examiner contends that Russell-Jones et al. teaches that foreign T-cell epitopes derived from diphtheria toxoid were known in the art, and that Russell-Jones et al. teaches that Trat T-cell epitopes are inserted into proteins, wherein the insertion of the peptides increases the antibody response into which the Trat peptide has been inserted. (Office Action at 12-13.) The Examiner relies on Dean et al. solely to support that somatostatin is a pathogenic self-protein because of its recognized role in a variety of diseases. The Examiner concludes that one of skill in the art would have been motivated to combine these teachings. (*Id*. at 13.)

Applicant traverses this rejection. Russell-Jones et al. does not teach or suggest all of the limitations of Applicant's claimed invention. Nowhere does

Russell-Jones et al. teach or suggest ***substituting*** any T-cell epitope into a ***self-protein***, as recited in the pending claims. Moreover, Russell-Jones et al. does not teach or suggest substituting any of the T-cell epitopes recited in Applicant's claims into a self-protein. In addition, Russell-Jones et al. does not teach or suggest that a self-protein with a T-cell epitope substituted into it can induce an autoantibody response as evidenced by antibody binding to the unmodified self-protein. Thus, Russell-Jones et al. does not teach or suggest making Applicant's invention. Dean et al. does not remedy these deficiencies. Accordingly, the rejection should be withdrawn for these reasons.

The Examiner argues that Russell-Jones et al. teaches that "Trat T cell epitopes are inserted into proteins, wherein the insertion of said peptide increases the antibody response against the protein into which Trat has been inserted (see page 4, lines 24-26 and Abstract)." (Office Action at 11.) Neither the Abstract nor page 4, lines 24-26, of Russell-Jones et al. supports the Examiner's conclusion. The Abstract of Russell-Jones et al. does not mention the insertion of any Trat T cell epitopes. Moreover, page 4, lines 24-26, only mentions generating high antibody titers to molecules "attached" to Trat, not molecules into which Trat epitopes are inserted. Moreover, none of the working examples in Russell-Jones et al. support that that the insertion of Trat T cell epitopes increases the antibody response against the protein into which the Trat epitope has been inserted. In Example 3 of Russell-Jones et al., ***conjugates*** of Trat with a Hepatitis antigen were made. Antibody responses to the Trat-Hepatitis antigen conjugate were higher than the response to a diphtheria toxin-

Hepatitis antigen conjugate. No insertions of a Trat peptide were made. In Example 4, Trat peptides were ***conjugated*** to HIV-1 gp120, and antibody responses were demonstrated. Once again, no insertions of a Trat peptide were made. Example 5 of Russell-Jones et al. is a *prophetic* example of removing suppressor regions in HIV-1 gp120 and replacing them with Trat epitopes. However, no insertions of a Trat peptide were made. Since Russell-Jones et al. did not make or assess any Trat T cell epitopes inserted into proteins, Russell-Jones et al. does not support the Examiner's argument that that such an insertion would increase the antibody response against the protein into which Trat has been inserted. Accordingly, the Examiner's argument is in error.

Applicant further points out that substitution of one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes, as recited in Applicant's pending claims, is not the same as inserting a T-cell epitope. Substitution preserves the overall secondary and tertiary structure of the self-protein to a large extent. (Specification at 3, lines 26-30.) It is the deletion of the self-protein sequences followed by the ***substitution*** of these sequences that minimally obscures the tertiary structure of the self-protein. (*Id.* at 10, lines 9-11.) The same cannot be said of the simple insertion of a T-cell epitope into a self-protein without deleting any self-protein sequences.

Furthermore, Russell-Jones et al. provides no expectation of success since Russell-Jones et al. never actually made a modified self-protein containing a T-cell epitope substituted into the self-protein. In fact, Russell-Jones et al. never made any modified self-protein whatsoever. Thus, Russell-Jones et al.

cannot provide any expectation that such a modified self-protein would induce an autoantibody response to the unmodified self-protein, as recited in Applicant's pending claims. Only Applicant's specification provides this expectation of success. Accordingly, the rejection should be withdrawn for these additional reasons.

To support the rejection, the Examiner relies on the Supreme Court's decision in *KSR*, stating: "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." (Office Action at 13.) The Examiner's reliance on this statement from KSR is in error. Russell-Jones et al. never actually made a modified self-protein containing a T-cell epitope from Trat substituted into the self-protein. Thus, a person of ordinary skill in the art would not have recognized that the insertion of any other T-cell epitope would induce an autoantibody response to the unmodified self-protein, as recited in Applicant's pending claims. It is only Applicant's specification that allows the skilled artisan make such a conclusion.

The rejection for obviousness over Russell-Jones et al. in view of Dean et al. should be withdrawn. The cited references do not teach or suggest all of the limitations of the pending claims. Also, the cited references do not provide any expectation of success. Accordingly, the pending claims cannot be obviousness over Russell-Jones et al. in view of Dean et al., and Applicant respectfully requests withdrawal of the rejection.

Claim 101 was rejected under 35 U.S.C. § 103(a) as being obvious over Russell-Jones et al. (WO 92/05192) in view of Dean et al. (U.S. Patent 5,716,596) as applied to claims 85-87 *supra*, and further in view of Hellman et al. (WO 93/05810) and Le et al. (U.S. Patent 5,698,195). The Examiner relies on Russell-Jones et al. and Dean et al. as rendering obvious the claimed invention except for the use of TNFα. The Examiner contends that Hellman et al. teaches conjugation of a self-protein to a carrier recognized by T helper cells to elicit antibodies and that Le et al. teaches the use of antibodies against TNFα to treat TNFα-mediated diseases.

Applicant traverses the rejection for the reasons presented *supra* with respect to the rejection over Russell-Jones et al. in view of Dean et al. In addition, neither Hellman et al. nor Le et al. remedies the deficiencies noted *supra*. That is, neither Hellman et al. nor Le et al. teaches or suggests ***substituting*** any T-cell epitope into a ***self-protein***, as recited in the pending claims. Moreover, neither Hellman et al. nor Le et al. teaches or suggests substituting any of the T-cell epitopes recited in Applicant's claims into a self-protein. In addition, neither Hellman et al. nor Le et al. teaches or suggests that a self-protein with a T-cell epitope substituted into it can induce an autoantibody response as evidenced by antibody binding to the unmodified self-protein. Thus, Applicant's claimed invention cannot be obvious over Russell-Jones et al. in view of Dean et al. and further in view of Hellman et al. and Le et al., and Applicant respectfully requests withdrawal of the rejection.

Applicant submits that this application is in condition for allowance. If the Examiner believes that issues remain to be addressed before a Notice of Allowance, Applicant respectfully requests that the Examiner contact the undersigned to discuss any outstanding issues.

Respectfully submitted,

Law Office of Salvatore Arrigo

Dated: May 15, 2009

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